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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/503,387	02/14/2000	Samantha J. Busfield	7853-178	6531

20583 7590 03/26/2002

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EXAMINER
HUYNH, PHUONG N

ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 03/26/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/503,387	BUSFIELD ET AL.	
	Examiner	Art Unit	
	" Neon" Phuong Huynh	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *Three* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)[·] Responsive to communication(s) filed on *1/25/01; 6/20/01*.

2a)[ ] This action is **FINAL**. 2b)[X] This action is non-final.

3)[ ] Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)[·] Claim(s) *24-70* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)[ ] Claim(s) _____ is/are allowed.

6)[·] Claim(s) *24-26,29, 36-52 and 54-70* is/are rejected.

7)[·] Claim(s) *27,28,30-35 and 53* is/are objected to.

8)[ ] Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)[ ] The specification is objected to by the Examiner.

10)[ ] The drawing(s) filed on _____ is/are: a)[ ] accepted or b)[ ] objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)[ ] The proposed drawing correction filed on _____ is: a)[ ] approved b)[ ] disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)[ ] The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)[ ] Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)[ ] All b)[ ] Some * c)[ ] None of:

1 [ ] Certified copies of the priority documents have been received.

2 [ ] Certified copies of the priority documents have been received in Application No. _____.

3.[ ] Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)[ ] Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) [ ] The translation of the foreign language provisional application has been received.

15)[ ] Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) [·] Notice of References Cited (PTO-892)
2) [·] Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) [·] Information Disclosure Statement(s) (PTO-1449) Paper No(s) *4,9*.
4) [ ] Interview Summary (PTO-413) Paper No(s). _____.
5) [ ] Notice of Informal Patent Application (PTO-152)
6) [ ] Other: .

DETAILED ACTION

1. Claims 24-70 are pending.

2. Applicant's election with traverse of Group I, Claims 24-64 (now Claims 24-70), drawn to antibody, filed 6/20/01, is acknowledged. The traversal is on the grounds that (1) Groups I and III are not distinct and a search of Groups I and III would not be a serious burden on the examiner. Upon reconsideration, Group III has been rejoined with Group I. Therefore, the requirement of Group I (now claims 24 to 70) and Group II is still deemed proper and is therefore made FINAL.

3. Claims 24-70, drawn to antibody that binds to SEQ ID NO: 3 are being acted upon in this Office Action.

4. Applicant should amend the first line of the specification to update the relationship between the instant application and 9/345,468, filed 6/30/1999, which is now Pat No. 6,245,527.

5. The drawings, filed 2/14/00, are not approved. Please see enclosed PTO 948, Notice of Draftsperson's Patent Drawing Review. Appropriate action is required.

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 29, 36-52, 54 and 57-70 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling only for (1) a composition of substantially purified antibodies or fragment thereof which antibodies bind to a polypeptide comprising an amino acid sequence of SEQ ID NO: 3 or the amino acid sequence encoded by the cDNA insert of the plasmid deposited with ATCC as Accession Number 207180 wherein said composition contains human antibodies, (2) an isolated non-human antibody or fragment thereof which antibodies bind to a polypeptide comprising an amino acid sequence of SEQ ID NO: 3 or the amino acid sequence encoded by the cDNA insert of the plasmid deposited with ATCC as Accession Number 207180 wherein said

antibody is a monoclonal antibody or a humanized antibody, (3) A monoclonal antibody or fragment thereof which specifically binds to a polypeptide comprising an amino acid sequence of SEQ ID NO: 3 or the amino acid sequence encoded by the cDNA insert of the plasmid deposited with ATCC as Accession Number 207180 wherein said antibody is a human antibody, a humanized antibody, a chimeric antibody, said antibody is conjugated to a therapeutic moiety or linked to a detectable substance such as the ones recited in claim 35 (4) *an* antibody Fc region fusion polypeptide comprising an antibody Fc region linked to the amino acid sequence of SEQ ID NO: 3 or the amino acid sequence encoded by the cDNA insert of the plasmid deposited with ATCC as Accession Number 207180 and (5) and a kit or composition comprising said antibody or said Fc fusion polypeptide mentioned above for diagnosis, screening assays and targeting therapeutic agents to the platelet receptor, does not reasonably provide enablement for (1) *any* substantially purified antibody or any fragment thereof which specifically binds to *any* extracellular domain of the amino acid sequence of SEQ ID NO: 3 wherein the extracellular domain "comprises" amino acid residues 21 to 269 of SEQ ID NO: 3 (2) the said extracellular domain "comprises" an immunoglobulin-like domain wherein the immunoglobulin domain "comprises" amino acid residues 48 to 88 or 134 to 180 of SEQ ID NO: 3, (3) the said antibody is *any* polyclonal antibody, *any* monoclonal antibody, *any* chimeric antibody, *any* humanized antibody, *any* human antibody, the said antibody is conjugated to any therapeutic moiety or linked to *any* detectable substance such as the ones recited in claim 47, (4) *any* antibody Fc region fusion polypeptide comprising an antibody Fc region linked to *any* fragment of at least 15 amino acid residues of the amino acid sequence of SEQ ID NO: 3, (5) the said antibody Fc region fusion polypeptide wherein the amino acid sequence "comprises" an extracellular domain of the amino acid sequence of SEQ ID NO: 3 wherein the extracellular domain "comprises" amino acid residues 21 to 269 of SEQ ID NO: 3 or the said extracellular domain "comprises" an immunoglobulin-like domain, (6) *any* kit comprising any antibody or fragment thereof mentioned above and instructions for use, (7) *any* pharmaceutical composition comprising *any* antibody or fragment thereof mentioned above and a pharmaceutical acceptable carrier as recited in claims 61 and 63, (8) *any* pharmaceutical composition comprising *any* antibody or fragment thereof mentioned above, *any* therapeutic moiety, and a pharmaceutically acceptable carrier as recited in claims 62 and 64, (9) *any* method of making said antibody mentioned above comprising immunizing a mammal any fragment of at least 15 amino acid residues of *any* amino acid sequence of SEQ ID NO: 3 as recited in claims 65-70. The specification does not enable any

person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in **scope** with these claims.

Factors to be considered in determining whether undue experimentation is required to practice the claimed invention are summarized *In re Wands* (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). The factors most relevant to this rejection are the scope of the claim, the amount of direction or guidance provided, the lack of sufficient working examples, the unpredictability in the art and the amount of experimentation required to enable one of skill in the art to practice the claimed invention. The specification disclosure is insufficient to enable one skilled in the art to practice the invention as broadly claimed without an undue amount of experimentation.

The specification discloses only (1) a composition of substantially purified antibodies or fragment thereof which antibodies bind to a polypeptide comprising an amino acid sequence of SEQ ID NO: 3 or the amino acid sequence encoded by the cDNA insert of the plasmid deposited with ATCC as Accession Number 207180 wherein said antibody is conjugated to a therapeutic moiety for targeting therapeutic agent to the platelet receptor, (2) the said antibody is linked to a detectable substance for diagnosis and screening assays and (3) a kit comprising said antibody for diagnosis and screening assays.

The specification does not reasonably provide enablement for *any* substantially purified antibody or any fragment thereof which specifically binds to *any* extracellular domain of the amino acid sequence of SEQ ID NO: 3 wherein the extracellular domain "comprises" amino acid residues 21 to 269 of SEQ ID NO: 3, or the said extracellular domain "comprises" an immunoglobulin-like domain wherein the immunoglobulin-like domain "comprises amino acid residues 48 to 88 or 134 to 180. The term "comprises" is open-ended. It expands the extracellular domain and the immunoglobulin-like domain of the amino acid sequence of SEQ ID NO: 3 to include additional amino acids at either end, in addition to the specific amino acid residues which already recited in SEQ ID NO: 3.

Ngo *et al* teach that the amino acid positions within the polypeptide/protein that can tolerate change such as conservative substitution or no substitution, addition or deletion which are critical to maintain the protein's structure/function will require guidance (see Ngo et al., 1994, The Protein Folding Problem and Tertiary Structure Prediction, pp. 492-495). Given the indefinite number of undisclosed amino acid residues to be added to the immunoglobulin-like domain or the immunoglobulin-like domain, the insufficient guidance and working examples,

predicting what changes can be made to the amino acid sequence of SEQ ID NOS: 3 that after insertion and/or modification will retain both structure and have similar function as SEQ ID NOS: 3 is unpredictable. Since the extracellular domain and the immunoglobulin-like domains of SEQ ID NO: 3 are not enabled, it follows that the binding specificity of said antibody is not specific. Therefore, any antibody such as the ones recited in claims 40-44 that are made with any undisclosed polypeptide are not enabled.

It is well known in the art at the time the invention was made that antibody epitopes (B cell epitopes) are not linear and are comprised of complex three-dimentional array of scattered residues which will fold into specific conformation that contribute to binding (See Kuby 1994, page 94, in particular). Immunization with a peptide comprising a contiguous amino acid sequence of 8 amino acid residues versus a protein derived from a full-length polypeptide may result in **antibody specificity** that differs from antibody specificity directed against the native full-length polypeptide. Without the specific amino acid residues, it is unpredictable to determine which antibody response generated from a peptide (fragment) will have the same antibody specificity as an antibody generated from the full length polypeptide or protein of SEQ ID NOS: 3, in turn, would be useful for *any* purpose. Given the indefinite number of undisclosed amino acids, it follows that the method of making any antibodies such as the ones recited in claims 40-44 is not enabled. Since antibody is not enabled, it follows that *any* therapeutic moiety and *any* detectable substance to be conjugated to said antibody, *any* pharmaceutical composition comprising said antibody and the method of making said antibody are not enabled. Further, there is insufficient guidance and in vivo working examples of any "pharmaceutical composition" comprising any antibody mentioned above for treating any specific diseases. In the absence of in vivo data, a pharmaceutical composition is unpredictable for the following reasons: (1) efficacy of the antibody or Fc fusion polypeptide has not been definitively demonstrated; (2) it is not always possible to extrapolate directly from in vitro experiments to in vivo treatment of all disease; (3) adverse reactions may resulted.

Likewise, the antibody Fc region fusion polypeptide recited in claims 48-52 is not enabled for the same reasons given above. The term "comprises" is open-ended. It expands the extracellular domain and the immunoglobulin-like domain of the amino acid sequence of SEQ ID NO: 3 to include additional amino acids at either end, in addition to the specific amino acid residues which already recited in SEQ ID NO: 3. Given the indefinite numbers of undisclosed amino acid residues, it is unpredictable which Fc fusion polypeptide would have the same

structure and function as the Fc fusion polypeptide comprising an antibody Fc region linked to SEQ ID NO: 3.

In re wands, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988), the decision of the court indicates that the more unpredictable the area is, the more specific enablement is necessary. In view of the quantity of experimentation necessary, the lack of in vivo working examples, the unpredictability of the art, the in sufficient guidance in the specification and the breadth of the claims, it would take an undue amount of experimentation for one skilled in the art to practice the claimed invention.

8. Claims 29, 36-52, 54 and 57-70 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention.

The specification does not reasonably provide a **written description** of (1) *any* substantially purified antibody or any fragment thereof which specifically binds to *any* extracellular domain of the amino acid sequence of SEQ ID NO: 3 wherein the extracellular domain "comprises" amino acid residues 21 to 269 of SEQ ID NO: 3 (2) the said extracellular domain "comprises" an immunoglobulin-like domain wherein the immunoglobulin domain "comprises" amino acid residues 48 to 88 or 134 to 180 of SEQ ID NO: 3, (3) the said antibody is *any* polyclonal antibody, *any* monoclonal antibody, *any* chimeric antibody, *any* humanized antibody, *any* human antibody, the said antibody is conjugated to any therapeutic moiety or linked to *any* detectable substance such as the ones recited in claim 47, (4) *any* antibody Fc region fusion polypeptide comprising an antibody Fc region linked to *any* fragment of at least 15 amino acid residues of the amino acid sequence of SEQ ID NO: 3, (5) the said antibody Fc region fusion polypeptide wherein the amino acid sequence "comprises" an extracellular domain of the amino acid sequence of SEQ ID NO: 3 wherein the extracellular domain "comprises" amino acid residues 21 to 269 of SEQ ID NO: 3 or the said extracellular domain "comprises" an immunoglobulin-like domain, (6) *any* kit comprising any antibody or fragment thereof mentioned above and instructions for use, (7) *any* pharmaceutical composition comprising *any* antibody or fragment thereof mentioned above and a pharmaceutical acceptable carrier as recited in claims 61 and 63, (8) *any* pharmaceutical composition comprising *any* antibody or fragment thereof mentioned above, *any* therapeutic moiety, and a pharmaceutically acceptable carrier as recited in

claims 62 and 64, (9) *any* method of making said antibody mentioned above comprising immunizing a mammal any fragment of at least 15 amino acid residues of *any* amino acid sequence of SEQ ID NO: 3 as recited in claims 65-70.

The specification discloses only (1) a composition of substantially purified antibodies or fragment thereof which antibodies bind to a polypeptide comprising an amino acid sequence of SEQ ID NO: 3 or the amino acid sequence encoded by the cDNA insert of the plasmid deposited with ATCC as Accession Number 207180 wherein said antibody is conjugated to a therapeutic moiety for targeting therapeutic agent to the platelet receptor, (2) the said antibody is linked to a detectable substance for diagnosis and screening assays and (3) a kit comprising said antibody for diagnosis and screening assays.

Other than the specific antibody that binds to the specific amino acid sequence mentioned above, there is insufficient **written description** about the structure associated with function of *any* extracellular domain "comprises" amino acid residues 21 to 269 of SEQ ID NO: 3, *any* extracellular domain "comprises" an immunoglobulin-like domain wherein the immunoglobulin-like domain "comprises" amino acid residues 48 to 88 or 134 to 180 of SEQ ID NO: 3 or the amino acid sequence encoded by the cDNA insert of the plasmid deposited with ATCC as Accession Number 207180. The term "comprising" is open-ended. It expands the amino acid sequence to include additional amino acids at either end. Further, the specification discloses only two species of TANGO 268 polypeptide to which the antibody binds, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus. Thus, Applicant was not in possession of the claimed genus. *See University of California v. Eli Lilly and Co. 43 USPQ2d 1398.*

Applicant is directed to the Revised Interim Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

9. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

10. Claims 24-26, 36-40, 55 and 61-62 are rejected under 35 U.S.C. 102(b) as being anticipated by Sugiyama *et al* (Blood 69(6): 1712-1720, June 1987; PTO 1449).

Sugiyama *et al* teach a composition of substantially purified antibody such as autoantibody (human antibody) and fragment thereof such as F(ab')2 in PBS, which is a phosphate buffer saline solution and a pharmaceutical acceptable carrier, wherein the reference antibody specifically binds to a collagen receptor on platelet with an apparent molecular weight of 62 KDa from a patient with defective collagen-induced Platelet aggregation and autoimmune thrombocytopenia (See abstract, Materials and Methods, page 1717, column 1, in particular). The reference protein appears to be the same as the claimed polypeptide of SEQ ID NO: 3 that is predicted to be approximately 62 kDa as disclosed on page 3 line 35. Claims 36 and 37 are included in this rejection because the antibody binds to the platelet receptor that is expressed on the cell surface (extracellular domain) and the reference antibody inherently binds to amino acid residues 21 to 269. The term "comprising" is open-ended. It expands the extracellular domain to read on the full-length polypeptide. Claim 38 is included in this rejection because the reference collagen receptor is a member of the immunoglobulin super family having an immunoglobulin-like domain and the immunoglobulin domains are extracellular domain. Claim 40 is included in this rejection because autoantibody is a polyclonal antibody.

While the reference is silent that the protein to which the reference antibody binds has the same amino acid sequence of SEQ ID NO: 3, the specification on page 3, lines 31-35 discloses that the claimed polypeptide TANGO 268 is identical to GPVI; TANGO 268 and GPVI are both recognized by anti-GPVI antibodies and bind to Cvx. Therefore the claimed antibody appears to be the same as the prior art antibody. Since the Patent Office does not have the facilities for examining and comparing the antibodies of the instant invention to those of the prior art, the burden is on applicant to show that the prior art antibody is different from the claimed antibody. See In re Best, 562 F.2d 1252, 195 USPQ 430(CCPA 1977). Thus, the reference teachings anticipate the claimed invention.

11. Claims 24-26, 36-40, 55 and 61-62 are rejected under 35 U.S.C. 102(b) as being anticipated by Gibbins *et al* (FEBS Letters 413: 255-259, 1997; PTO 1449).

Gibbins *et al* teach a substantially purified antibody such as autoantibody anti-GPVI or fragment thereof such as F(ab')2 in Tris-HCl which is a buffer solution and a pharmaceutical acceptable carrier from a patient with defective collagen-induced Platelet aggregation such as autoimmune thrombocytopenia which specifically binds to glycoprotein VI (GPVI) on platelet (See Materials and Methods, first paragraph, page 256, first column, in particular). The reference surface protein is approximately 60 kDa (See page 256, column 1, Fig 1, arrow, in particular) appears to be the same as the claimed polypeptide of SEQ ID NO: 3 as disclosed on page 3 line 35. Claims 36 and 37 are included in this rejection because the antibody binds to the platelet receptor that is expressed on the cell surface (extracellular domain) and the reference antibody inherently binds to amino acid residues 21 to 269. The term "comprising" is open-ended. It expands the extracellular domain to read on the full-length polypeptide. Claim 38 is included in this rejection because the reference collagen receptor is a member of the immunoglobulin super family having an immunoglobulin-like domain and the immunoglobulin domains are extracellular domain. Claim 40 is included in this rejection because autoantibody is a polyclonal antibody.

While the reference is silent that the protein to which the reference antibody binds has the same amino acid sequence of SEQ ID NO: 3, the specification on page 3, lines 31-35 discloses that the claimed polypeptide TANGO 268 is identical to GPVI; TANGO 268 and GPVI are both recognized by anti-GPVI antibodies and bind to Cvx. Therefore the claimed antibody appears to be the same as the prior art antibody. Since the Patent Office does not have the facilities for examining and comparing the antibodies of the instant invention to those of the prior art, the burden is on applicant to show that the prior art antibody is different from the claimed antibody. See In re Best, 562 F.2d 1252, 195 USPQ 430(CCPA 1977). Thus, the reference teachings anticipate the claimed invention.

12. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 103(a) that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

13. This application currently names joint inventors. In considering Patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

14. Claims 36, 45-47, 54, 62 and 64 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sugiyama *et al* (Blood 69(6): 1712-1720, June 1987; PTO 1449) or Gibbins *et al* (FEBS Letters 413: 255-259, 1997; PTO 1449) each in view of Harlow *et al* (in Antibodies a Laboratory Manual, 1988, Cold Spring harbor laboratory publication, Cold Spring Harbor, NY, pages 321-358) or US Patent No 5,877,289, (March 1999PTO 892).

The teachings of Sugiyama *et al* and Gibbins *et al* have been discussed supra.

The claimed invention as recited in claims 33 and 45 differs from the references only by the recitation of the antibody is conjugated to a therapeutic moiety.

The claimed invention as recited in claims 34 and 46 differs from the references only by the recitation of the antibody is linked to a detectable substance.

The claimed invention as recited in claims 35 and 47 differs from the references only by the recitation of the detectable substance is an enzyme, a prosthetic group, a fluorescent material, a luminescent material, a bioluminescent material and a radioactive material.

The claimed invention as recited in claim 54 differs from the references only by the recitation of a kit comprising an antibody or fragment thereof and instruction for use.

The claimed invention as recited in claims 62 and 64 differs from the references only by the recitation of a therapeutic moiety.

Harlow *et al* teach methods of labeling any antibody with a detectable substance such as ^{125}Iodine which is a radioactive material widely used for autoradiographic detection and a therapeutic moiety for nuclear medicine (See page 591 and 324, in particular), an enzyme label such as alkaline phosphatase (page 597, in particular), horseradish peroxidase, a fluorescein label such as isothiocynate (FITC) (See page 353, in particular). The advantages of Iodine labeling is that it is easy to quantitative, easy to label directly whereas the advantages of antibody labeled with enzyme include long shelf life, high sensitivity, direct visualization possibility (See page

322, in particular). The fluorescein labeled antibodies offer the advantages of longer shelf life, good resolution, and quantitative analysis.

The '289 patent teaches conjugated antibody such as VEGF antibody conjugated to one or more therapeutic agents such as immunotoxin, chemotherapeutic drugs or diagnostic agents, various tissues factors, biological agents, or enzymes via cleavable peptide linkers as a fusion protein (See column 9-13; column 48-53; column 54-57 paragraph recombinant fusion proteins; column 44, paragraph 2; column 74, paragraph recombinant human truncated tissue factor; column 83-92) and a pharmaceutical composition comprising additional therapeutic agents such as cyclosporin (See column 12, lines 31-52, columns 72-73, Therapeutic Kits). The '289 patent teaches conjugated antibodies or specific targeting ligands could be used to direct the therapeutic agents to the site of interest (See column 45, lines 40-55, in particular). The '289 patent further teaches the method of detection is conveniently provided in the form of a kit that is a packaged collection of reagents or combination of other assay components as necessary and appropriate for the needs of the user (See columns 72-73, in particular).

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to link or conjugate the antibody to a detectable substance as taught by Harlow *et al* or therapeutic moiety as taught by '289 patent with the antibody as taught by Sugiyama *et al* and Gibbins *et al* and place the labeled antibody in a kit as taught by '289 patent for convenience and commercial expedience. From the teaching of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to do this because Harlow *et al* teach the advantages of Iodine labeling is that it is easy to quantitative, easily to labeling directly whereas the advantages of antibody labeled with enzyme include long shelf life, high sensitivity, direct visualization possibility; the fluorescein labeled antibodies offer the advantages of longer shelf life, good resolution, and quantitative analysis (See page 322, in particular). The '289 patent teaches conjugated antibodies or specific targeting ligands could be used to direct the therapeutic agents to the site of interest (See column 45, lines 40-55, in particular). A kit will allow for ease of use for the practitioner since all the necessary reagents, standard and instructions for use are included in a kit as taught by '289 (See column 9, lines 46-51, in particular).

15. **INFORMATION ON HOW TO EFFECT DRAWING CHANGES**

1. Correction of Informalities -- 37 CFR 1.85

New corrected drawings must be filed with the changes incorporated therein. Identifying indicia, if provided, should include the title of the invention, inventor's name, and application number, or docket number (if any) if an application number has not been assigned to the application. If this information is provided, it must be placed on the front of each sheet and centered within the top margin. If corrected drawings are required in a Notice of Allowability (PTOL-37), the new drawings **MUST** be filed within the **THREE MONTH** shortened statutory period set for reply in the "Notice of Allowability." Extensions of time may NOT be obtained under the provisions of 37 CFR 1.136 for filing the corrected drawings after the mailing of a Notice of Allowability. The drawings should be filed as a separate paper with a transmittal letter addressed to the Official Draftsperson.

2. Corrections other than Informalities Noted by Draftsperson on form PTO-948.

All changes to the drawings, other than informalities noted by the Draftsperson, **MUST** be made in the same manner as above except that, normally, a highlighted (preferably red ink) sketch of the changes to be incorporated into the new drawings **MUST** be approved by the examiner before the application will be allowed. No changes will be permitted to be made, other than correction of informalities, unless the examiner has approved the proposed changes.

3. Timing of Corrections

Applicant is required to submit acceptable corrected drawings within the time period set in the Office action. See 37 CFR 1.85(a). Failure to take corrective action within the set period will result in **ABANDONMENT** of the application.

16. Claims 27-28, 30-35 and 53 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

17. Claims 29-35 are free of art.

18. Any inquiry concerning this communication or earlier communications from the examiner should be directed to "Neon" Phuong Huynh whose telephone number is (703) 308-4844. The examiner can normally be reached Monday through Friday from 9:00 am to 6:00 p.m. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

19. Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform to the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-7401.

Phuong N. Huynh, Ph.D.
Patent Examiner
Technology Center 1600
March 25, 2002

CHRISTINA Y. CHAN
SUPERVISORY PATENT EXAMINER
GROUP ~~1600~~ 1640